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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,004	01/24/2002	Kenneth J Breslauer	RU-0124	6792

26259 7590 08/13/2002

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EXAMINER
MAUPIN, CHRISTINE L

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,004	Applicant(s) BRESLAUER ET AL.	
	Examiner Christine L. Maupin	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s) _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☒ Other: *Detailed Action*.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-32, are drawn to methods for screening nuclei acid duplex stability.

Group II, claim(s) 33-37, are drawn to kits comprising labeled donor and acceptor FET-labeled nucleic acids.

The inventions listed as groups do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The claims lack a special technical feature because there are at least two references which anticipate claim 1, Malmqvist et al US Patent No. 5,972,612 issued 26th, October 1999, which is in the international search report. A special technical feature is a novelty, which defines the invention over the prior art. Here, because the product claims of the kits containing labeled duplex nucleic acids strands with known thermodynamic constants and or polymorphism with complementary lacks novelty over the prior art, there is no special technical feature and a lack of unity requirement is proper.

During a telephone conversation with Kathleen Tyrrell on August 5th, 2002 a provisional election was made to elect Group I, claim(s) 1-32 with traverse to prosecute

the invention of Group II, claim(s) 33-37. Applicant in replying to this Office action must make affirmation of this election. Claim(s) 33-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is requested to expedite prosecution.

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

Claim Objections

Claims 16-29 are objected to under 37 CFR 1.75(c) as being in improper form because a series of multiple dependent claims depending upon each other. See MPEP § 608.01(n). For example claim 17 is dependent upon claim 16 that, is a multiply dependent claim itself, which is dependent upon another multiple dependent claim such

as claim 14. Accordingly, the claim(s) 16-29 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim1-17, and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant application the claims describing the competitive read as following: It is confusing to one of ordinary skill in the art to determine if the target strand is a single strand in a solution along with a duplex strand or if one of the strands of the duplex is the target strand. It is indefinite as to the number of single strands that are present in the initial solution of step a, or which strand is the target strand and which stand is in competition for the target. Clarification of the number of strands in the initial solution and which strand is the target and which strand is the focus of the target strand is necessary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albrecht et al, US Patent No. 6,265,163 issued July 24th, 2001, in view of Drmanac et al, US Patent No. 5,525,464 issued July 2nd, 1996.

The instant application teaches method for screening for a nucleic acid duplex stability by competitive equilibra comprising:

a) producing a solution containing a known amount of an initial nucleic acid duplex with known stability, said initial nucleic acid duplex comprising a first nucleic acid strand having a sequence wholly or in part homologous to a target strand and having a second nucleic acid strand having a sequence wholly or partly homologous to a target strand and a second strand wholly or in part complementary to the target strand;

(b) titrating the solution with a second solution comprising a known concentration of the target nucleic acid strand which competes with the first nucleic acid strand for binding to the second nucleic acid strand, said target nucleic acid strand being single- or double-stranded;

(c) subjecting the titrated solution to conditions which disrupt the initial duplex and any duplex or triplex formed between the target strand and the second nucleic acid strand, but which do not disrupt the target strand when double-stranded;

(d) subjecting the titrated solution to conditions which promote duplex or triplex formation; and

(e) monitoring the titrated solution for changes in the amount of initial nucleic acid duplex formed as a function of the amount of target nucleic acid strand added;

Albrecht et al, US Patent No. 6,265,163 issued July 24th, 2001 teaches the use of a method for competitive hybridization (see column 17, lines 13-49) between the labeled DNA strands derived from the plurality of cells or tissues is carried out by the following steps of a competitive methods comprising of:

a) applying equal quantities of the labeled DNA strands from each such source to the microparticles loaded with the reference DNA population in a conventional hybridization reaction; (column 17, lines 14-18)

b) the particular amounts of labeled DNA strands added to the competitive hybridization reaction vary widely depending on the embodiment of the invention. Factors influencing the selection of such amounts include the quantity of microparticles used, the type of microparticles used, the loading of reference DNA strands on the microparticles, the complexity of the populations of labeled DNA strands, and the like. Hybridization is competitive in that differently labeled DNA strands with identical, or substantially identical, sequences compete to hybridize to the same complementary reference DNA strands; (column 17, lines 18-28)

c) the competitive hybridization conditions are selected so that the proportion of labeled DNA strands forming duplexes with complementary reference DNA strands reflects, and preferably is directly proportional to, the amount of that DNA strand in its

population in comparison with the amount of the competing DNA strands of identical sequence in their respective populations; (column 17, lines 28-35)

d) a first and second differently labeled DNA strands with identical sequence are competing for hybridization with a complementary reference DNA strand such that the first labeled DNA strand; (column 17, lines 35-38)

e) monitoring and determining the first labeled DNA strand is at a concentration of 1 ng/μl and the second labeled DNA strand is at a concentration of 2 ng/μl, then at equilibrium it is expected that one third of the duplexes formed with the reference DNA would include first labeled DNA strands and two thirds of the duplexes would include second labeled DNA strands and two thirds of the duplexes would include second labeled DNA strands. (column 17, lines 38-43)

Therefore teach that quantification may be obtained from competitive hybridization or an association-disassociation relationship.

Albrecht et al., does not specifically teach the use of label or fluorescent DNA strands to calculate the values for $\Delta H°$, $\Delta G°$, and $\Delta S°$ as a function of fluorescent decay.

Drmanac et al., teaches methods for determining the hybridization stability and its relationship to other thermodynamic properties as related to the function of competitive equilibria and that the stability is related to the uninterrupted Watson-Crick base paring (column 5, line 17-26). Drmanac et al., further teaches the theoretical (column 14, line, 22 thru column 17, line 58) principles of oligonucleotide hybridization to filter bound target nucleic acids only a few nucleotides longer than the probe in conditions of probe excess is a pseudo-first order reaction with respect to target

concentration. Breslauer et al., Proc. Natl. Acad. Sci, USA (1986) Vol.83, pages 3746-3750, teaches that a given set of solution conditions, the relative stability of the DNA duplex structure may be predicted such as $\Delta H°$, $\Delta G°$, and $\Delta S°$ (see abstract, and results section page 3747, particularly last paragraph of the page in column 2). Therefore Drmanac et al., teaches that methods in by which the concentrations and total volumes of the nucleic acids in each solution are stringently controlled.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of measuring duplex stability as taught by Breslauer with the competitive hybridization of Albrecht since an ordinary practioner would want to optimize the hybridization of Albrecht by measuring the ideal duplex stability of probes. Especially motivated by Breslauer's statements (abstract) "this capability would prove valuable in predicting the stability of gene-probe complex, setting optimal conditions for hybridization, deciding on the minimum length of a probe, predicting the influence of specific transversion or transition on the stability of an affected DNA region, and predicting the relative stabilities of local domains within a DNA duplex".

It would also be prima facie obvious to one of ordinary skill in the art at the time the invention was conceptualized to utilized the temperature dependent melting procedures of well controlled solutions and volumes and the working theoretical principles and procedures of Drmanac utilizing the methods of competitive binding assays of Albrecht to obtain the thermodynamic stability data values of $\Delta H°$, $\Delta G°$, and $\Delta S°$ by using temperature to alter the hybridization rate, because the rate is proportional

to the concentration the nucleic acids, which in turn may be measure at different temperature, which may then be use to determine the E_a (energy of activation) by solving a linear equation in which the slope is equal to E_a. The van't Hoff Equation may then be used to calculate the $\Delta H° = -R(\partial \ln K/\partial(1/T)$. Since the concentrations are known then the volume of the solution are known and the equilibrium constants may be calculated with respect to the law of mass action $K_c=[C]^c[D]^d/[A]^a[B]^b$. Although Albrecht does not disclose any rigorous calculation of the stability of the competitive hybridizations, it would be motivating and apparent to one of ordinary skill in the art to note that the stability would need to be necessary to carry the competitive hybridization to completion or in the least to be altered to accomplish a competitive hybridization. Therefore been able to predict the likely outcome of competitive nucleic acid hybridiations.

Further, one of ordinary skill in the art would be motivated to use fluorescent labeled DNA strands for detection of hybridization and mismatches or other anomalies by combining the methods of Albrecht and Drmanac, since fluorescent labels can replace radioactive labels, which are hazardous, burdensome waste material, environmentally safer, and can demonstrate changes in the spectral due to changes in concentration (Drmanac, column 2, 47-68). Still, further, one of ordinary skill in the art would also recognized that the impact resonance or Förster transfer would be as a valuable indicator of base pair mismatching, polymorphisms or other anomalies due to the longer distance which would incur, which is well know in the art, between the donor and acceptor due to the fact that the efficiency of the transfer is equal to

$$Eff = \frac{r_0^6}{r_0^6 + r^6}.$$

Therefore, the larger or more pronounced the mismatch the longer the lifetime of the energy transfer (Tinoco, Jr. et al Physical Chemistry, Principles and Applications in Biological Sciences (1978) Prentice Hall, Englewood Cliffs, NJ p.452-453.)

Conclusion

Claims 1-15, 30-32 are rejected and claims 16-29 are objected to due to improper multiple dependencies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine L. Maupin; whose telephone number is (703) 308-3617 and fax number is (703) 746-7641.

The examiner is normally in the office between the hours of 9:30 a.m. and 5:30 p.m., and telephone calls either in the morning or the mid-afternoon are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1234.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the U.S.P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 308-4242 or (703) 308-2724. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

August 12, 2002

Christine L. Maupin
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER